A PILOT PROJECT TO STUDY THE FEASIBILITY OF INTERDIGITATING HIGH DOSE RATE BRACHYTHERAPY WITH CONCURRENT CHEMOIRRADIATION IN CARCINOMA CERVIX.

CERTIFICATE

This is to certify that "A pilot project to study the feasibility of interdigitating High Dose Rate brachytherapy with Concurrent Chemoirradiation in carcinoma cervix" is an original work by Dr David Mathew in partial fulfillment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in March 2010.

GUIDE ----------

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TABLE OF CONTENTS

AIM

I AIM OF THE STUDY

Primary objectives:

1. To assess the feasibility of interdigitating High Dose Rate (HDR) brachytherapy with External Radiotherapy.
2. To evaluate the acute toxicity of interdigitating HDR brachytherapy with external radiotherapy during the period of treatment.
3. To study the reasons for not being able to interdigitate brachytherapy with the external beam radiotherapy.

Secondary objective:

1. To assess the possibility of reduction in overall treatment time.

INTRODUCTION

II INTRODUCTION

Carcinoma of the cervix is one of the commonest malignancies among women in India.

About 1, 00, 000 women are diagnosed with cervical cancer each year.[1] Radiotherapy (both teletherapy and brachytherapy) constitutes an integral part in the management of cervical cancer. Teletherapy can be delivered by telecobalt or linear accelerator.[2,3] Meta - analysis reveals that with the addition of concurrent chemotherapy using platinum based drugs the overall absolute survival is increased by 12%.[4] Various studies indicate that the success of treatment depends on the completion of full treatment within 8 weeks. Several studies have shown that there is a decrease of overall survival by 1% per day beyond 8 weeks.[5] In view of this it is imperative to complete the full treatment including brachytherapy within 8 weeks. Since with HDR brachytherapy multiple applications are required, if done after completion of EBRT this would result in prolongation of treatment time beyond 8 weeks. Therefore many groups have tried to interdigitate brachytherapy with external radiotherapy.

The primary concern of HDR Brachytherapy is the potential late toxicity of large dose per fraction, which can be overcome through adequate fractionation.[3] Additionally in HDR, late tissue complications might be minimized more effectively than in LDR, because greater normal tissue displacement (e.g., bladder anteriorly and rectum posteriorly) is possible because of the short treatment times and available retraction devices. The risk of bladder and rectal complications depends upon the doses received by the bladder and the rectum.

The aim of this study is to assess the feasibility and tolerability of interdigitating HDR brachytherapy with External radiotherapy in carcinoma cervix in our patients.

REVIEW OF THE LITERATURE

III REVIEW OF LITERATURE

3.1Epidemiology

Carcinoma of the cervix is the 6th most common malignant neoplasm in human after carcinoma breast, lung, colorectal, endometrial and ovary. Carcinoma of the cervix is the second leading cause of female cancer deaths in the underdeveloped countries.[6] Carcinoma cervix is more common in women who had first intercourse at an early age, have a history of promiscuity and large number of pregnancies.[7, 8, 9]

The most common type of invasive cancer of the cervix is squamous cell carcinoma, with subtypes, papillary (squamotransitional) subtype, the verrrucous subtype and the lymphoepithelioma-like subtype[10]

3.2 Risk Factors

A retrospective analysis though surrounded by many controversies undertaken by Kapp et al, in an attempt to identify prognostically significant pretreatment factors showed that FIGO stage is an important prognostic factor along with other factors including patient age at diagnosis, pretreatment neutrophil count and hematocrit, uterine position, prior subtotal hysterectomy, histology, history of diabetes mellitus and number of pregnancies. When all other factors including stage was controlled for, increased tumor size was associated with decrease disease-free survival and local-regional control rates.[11]

Some of the studies which have reported prognostic factors and is suggested to be included in the staging system are depth of stromal invasion, tumor size, presence or absence of lymphatic vascular space invasion, pelvic lymph node status, tumor volume, endometrial extension of

cervical carcinoma, and parametrial involvement.[12] Other patient factors which have been extensively studied are the age[13] and the socioeconomic factor.[14] Medical factors include Anemia,[15] Tumor hypoxia. Others under consideration are arterial hypertension, fever, HIV.[16]

When we consider lymphatic spread and the various types of histology, positive lymph nodes are found in adenocarcinomas much higher than in squamous cell carcinoma, showing the difference in their behavior. It was also found by Korhonen et al that there is no significant difference in survival rate between pure adenocarcinoma, adenosquamous carcinoma, clear cell adenocarcinoma and adenocarcinoma. It was also found that the histological grade had a direct correlation to the survival rate; for grade I tumors it was about 60%, whereas for patients with grade IV tumors only about 10% survived. [17]

3.3 Pathology

Although squamous cell carcinoma is the most common type of carcinoma of cervix other histological types can also be seen. Given below is WHO classification of the various histological types.

Carcinoma of cervix--(WHO classification of cervical tumors)[18]

Epithelial tumors

Squamous lesions and precursors

Squamous cell carcinoma, not otherwise specified

1. Keratinizing
2. Nonkeratinizing

3. Basaloid
4. Verrucous
5. Warty (condylomatous)
6. Papillary (transitional)
7. Lymphoepithelioma-like
8. Squamotransitional
9. Early invasive (microinvasive) squamous cell carcinoma
10. Squamous intraepithelial neoplasia / lesions (SIL)
11. High grade (usually lumped with carcinoma in situ) or low grade
12. Cervical intraepithelial neoplasia (CIN) - *different terminology than SIL*
13. CIN 1 (mild dysplasia, low grade SIL)
14. CIN 2 (moderate dysplasia, high grade SIL)
15. CIN 3 (severe dysplasia, carcinoma in situ, high grade SIL)
16. Benign squamous cell lesions
17. Condyloma acuminatum
18. Squamous papilloma
19. Fibroepithelial polyp

Glandular tumors and precursors

1. Adenocarcinoma
2. Mucinous adenocarcinoma (endocervical, intestinal, signet ring, minimal deviation, villoglandular subtypes)
3. Endometrioid adenocarcinoma (may have squamous metaplasia)
4. Clear cell adenocarcinoma

5. Serous adenocarcinoma
6. Mesonephric adenocarcinoma
7. Early invasive adenocarcinoma
8. Adenocarcinoma in situ
9. Glandular dysplasia
10. Benign glandular lesions
11. Mullerian papilloma
12. Endocervical polyp
13. Other epithelial tumors
14. Adenosquamous carcinoma
15. Glassy cell carcinoma variant
16. Adenoid cystic carcinoma
17. Adenoid basal carcinoma
18. Neuroendocrine tumors
19. Carcinoid tumor
20. Atypical carcinoid tumor
21. High grade neuroendocrine carcinoma - small cell or large cell types
22. Undifferentiated carcinoma

Mesenchymal tumors and tumor like conditions

1. Leiomyosarcoma
2. Endometrioid stromal sarcoma, low grade
3. Undifferentiated endocervical sarcoma
4. Embryonal rhabdomyosarcoma (sarcoma botyroides)

5. Alveolar soft parts sarcoma
6. Angiosarcoma
7. Malignant peripheral nerve sheath tumor
8. Leiomyoma
9. Genital rhabdomyoma
10. Postoperative spindle cell nodule

Mixed epithelial and mesenchymal tumors

1. Carcinosarcoma (malignant mullerian mixed tumor)
2. Adenosarcoma
3. Wilms tumor
4. Adenofibroma
5. Adenomyoma
6. Melanocytic tumors
7. Malignant melanoma
8. Blue nevus

Miscellaneous tumors

Germ cell tumors (yolk sac tumor, dermoid cyst, mature cystic teratoma)

Lymphoid and hematopoietic

Malignant lymphoma (specify type)

Leukemia (specify type)

Secondary tumors

3.4 Clinical Presentation

Early invasive carcinoma of the cervix can be detected before it becomes symptomatic by cytological smears. Serosanguineous or yellowish, foul-smelling vaginal discharge may be noted in patients with invasive carcinoma, particularly with more advanced necrotic lesions. If chronic bleeding occurs, the patient may complain of fatigue or other symptoms related to anemia.

Pain, usually in the pelvis or hypogastrium, may be noted and could be caused by tumor necrosis or associated pelvic inflammatory disease. Some patients may complain of pain in the lumbosacral area, and in these cases the possibility of paraaortic lymph node involvement with extension in to the lumbosacral roots or hydronephrossis should be considered. Occasionally epigastric pain may be caused by metastasis to high para-aortic lymph nodes.

Urinary and rectal symptoms (hematuria, rectal bleeding) may appear in advanced stages as a consequence of invasion of the bladder or rectum by the neoplasm. [19]

3.5 Staging and workup

It is recommended that all patients with carcinoma cervix should be jointly evaluated by the radiation and gynecologic oncologist. Detailed history and physical examination of the patient including a pelvic examination should be done. Special attention to the supra clavicular nodal areas abdomen and liver should be carried out. Pelvic examination should include inspection of external genitalia, vagina and uterine cervix, rectal examination and bimanual palpation of the pelvis. Cystoscopy or rectosigmoidoscopy should be performed in all patients with stage IIB and more advanced disease and in those patients who gives a history of urinary or lower gastrointestinal tract complaints.[20]

Staging of Carcinoma of the uterine cervix is staged and managed by means of the International Federation of Gynecology and Obstetrics (FIGO) staging system. The FIGO staging system is determined preoperatively mainly by the clinical assessment. This was seen to be quit sufficient for early stage disease, but it has inherent inaccuracies in advanced stage disease. It does not take into account the nodal involvement. Though not routinely used in the developing countries, CT and MR imaging are widely used elsewhere to evaluate tumor size and extent, and nodal involvement. In this it was found that MR imaging is excellent for depicting invasive cervical carcinoma with objective measurement of tumor volume. It rules out conclusively parametrial invasion and stage IVA disease.[21]

Cervical cancer staging is the oldest staging in the literature, dating back to 1928. Classification of the Stages of Carcinoma of the Uterine Cervix is done by International Federation of Gynecology and Obstetrics. Since the initial staging was introduced by them, the staging for cervical cancer has undergone 7 revisions, last was in 1994. The controversies surrounding cervical cancer staging has contributed to yet another revision in 2009 and published in International journal of gynecology and obstetrics which is the official organ of the FIGO.[22]

The following is the recommended investigations for the work up of carcinoma of cervix;

Diagnostic work-up for carcinoma of the uterine cervix[23]

General	*History *Physical examination, including bimanual pelvic and rectal examinations
Diagnostic procedures	*Cytological smears(Papanicolaou) if not bleeding *Colposcopy *Conization (subclinical tumor) *Punch biopsies (edge of gross tumor, four quadrants) *Dilatation and curettage *Cystoscopy, rectosigmoidoscopy(stages IIB, III, and IVA
Radiographic Studies	Standard *Chest radiography *Intravenous pyelography *Barium enema (stages III and IVA and earlier stages if there are symptoms referable to colon or rectum) Complementary *Lymphangiography *Computed tomography or magnetic resonance imaging *Positron emission tomography scan(optional)
Laboratory studies	*Complete blood count *Blood chemistry *Urinalysis

Cytology

The American cancer society has recommended that asymptomatic women 20 years of age and older, and those younger than 20 yrs who are sexually active have a papanicolaou smear annually for 2 consecutive yrs and at least 1 every 3 yrs until the age of 65.[24] Women who have high risk for development of cervical carcinoma should have a yearly smear. If the cytological smear shows dysplasia and malignant cells colposcopy directed biopsies should be carried out immediately.

Colposcopy

Colposcopy is useful in detecting majority of the early cervical lesions if it is combined with cytology examination and biopsy of grossly abnormal size.

Conisation

It is performed in specific situations when an endocervical tumor is suspected, when the entire lesion cannot be seen by colposcope, when the diagnosis of microinvasive carcinomas made on biopsy or the patient is not reliable for continuous follow up. [25]It involves conical removal of large portion of exocervix and endocervix. At least 50 percent of endocervical canal should be removed without compromising the internal sphincter. Curettage of the remaining endocervical canal should be carried out.

Biopsy

When a gross lesion of the cervix is present multiple punch biopsies are done from the suspect area, all four quadrants of the cervix and suspect area in the vagina. It is important to obtain tissue from the periphery of the lesion with some adjoining normal tissues.

Dilatation and Curettage

Fractional curettage of endocervical canal and endometrial is recommended to plan therapy for the possible extension of upper extension of tumor when indicated. [26]

Laboratory studies

Blood tests included serum for Biochemistry – creatinine and liver function tests, blood for Pathology-hemoglobin, total count with differentials, platelets, and Virology sample for Blood Borne Viruses, and urine analysis.

Radiological tests- Chest X-ray *(PA),* and intravenous pyelogram is recommended for all patients. A colon barium enema is advised for all patients with stage IIB and more advanced disease and in those patients who gives a history of urinary or lower gastrointestinal tract complaints.[27] Those who afford can do USG abdomen and pelvis (or CT) instead of the same.

Management for locally advanced (Stage 2b and 3b)

3.6 Treatment with radiotherapy

Radiotherapy is the mainstay of treatment in carcinoma of cervix. Radiotherapy is delivered by a combination of external beam photon therapy and brachytherapy. External irradiation is used to treat the whole pelvis and parametrium including the common iliac nodes whereas the central disease- cervix, vagina and the medial pat of the parametrium is primarily irradiated with the intracavitary sources.

External beam irradiation- It is delivered before intracavitary insertions in patients with a) bulky cervical lesions or tumors beyond stage IIA to improve the geometry of the intracavitary

application; b) exophytic easily bleeding tumors, c) tumors with necrosis or infection, d) parametrial involvement.[28]

Tumor Volume

It is important to deliver the adequate doses of irradiation not only to the primary tumor and to the pelvic lymph nodes. The common iliac bifurcation being cephalad to the lumbosacral prominence, the superior border of the pelvic portal should be at the L4/L5 inter space to include all of the external iliac and the hypogastric lymph nodes. This margin is extended to the L3/L4 interspace if common iliac nodes are to be covered. A 2 cm margin lateral to the bony pelvis is adequate. If there is no vaginal extension, the lower border of the portal is at the inferior border of the obturator foramen. If the vagina is involved, the entire length upto the introitus should be treated. In patients with tumor involving the distal half of the vagina, the portal fields should include the inguinal lymph nodes. The anterior border of the lateral field is kept 3 cm in front of the anterior surface of the L4 vertebral body or at the pubic symphisis and posteriorly at the S2/S3 junction. In locally advanced tumors the posterior border maybe extended to include the entire sacral hollow.[29]

3.7 Trials with radiotherapy alone

Denton et al did a study to investigate the UK prevalence of late, severe side-effects associated with radical radiotherapy for cancer of the cervix and associated factors. 53 departments in UK out of 55 participated in the study. There were 1558 patients with carcinoma of the cervix receiving radical radiotherapy. Late severe complications in the year 1993 was 6.1% (actuarial rate 8%) at 5 years. Only 4 out of the 91 patients who developed complications died as a result of their morbidity. There was no significant correlation of stage, centre size, surgery or radio

therapeutic approach with late morbidity. The only factor significantly associated with mortality was the FIGO staging.[30]

Yalman et al did a study to evaluate early and late radiation morbidity in patients with cervical or endometrial cancer treated by a combination of external radiotherapy (ERT) and intracavitary brachytherapy (IBRT). Early and late radiation morbidity were evaluated retrospectively using RTOG/EORTC criteria. Total doses at the vagina, bladder and rectum in operated cervix cancer patients were 60.51 Gy, 56.53 Gy and 55.67 Gy, respectively. BED for the same points were 79.77, 69.36 and 67.52, respectively for early effects and 124.74, 99.3 and 95.17, respectively for late effects. 38.1% developed early morbidity. Grade I and II bladder morbidity was the most common type. 30.9% developed late morbidity, vaginal morbidity being the most common type. Total doses at the vagina, bladder and rectum in inoperable patients were 70.92 Gy, 66.71 Gy and 62.38 Gy, respectively. BED for the same points were 97.43, 89.64 and 81.63, respectively for early effects and 159.3, 143.16 and 126.56, respectively for late effects. 39% developed acute morbidity which was grade I or II bladder morbidity in 95%. 61.7% developed late morbidity which was grade I-III vaginal morbidity in 94%. It concluded that patients with cervical or endometrial cancer can be treated safely by a combination of ERT and IBRT. However the patients should be assessed before, during and after treatment and at every period of follow-up to monitor the morbidity rate.[31]

Potter et al tried to compare small tumors against large tumors. The mean dose for brachytherapy was 16.2 Gy at the ICRU rectum reference point and 14.4 Gy at the ICRU bladder point. Taking into account the dose for EBT, the mean isoeffective dose at the ICRU rectum reference point was 69.9 Gy. Overall treatment time was six weeks for small tumors and eight weeks for large

tumors. The actuarial late complication rate for grades 3 and 4 was 2.9% for the bladder, 4.0% for the bowel, 6.1% for the rectum and 30.6% for the vagina. Overall toxicity was comparable to other reports. He recommended increasing the therapeutic window by integrating MRI into treatment planning, allowing for a highly individualized approach.[32]

3.8 Trials showing benefit of concurrent chemotherapy

NCI alert was issued in February 1999 based on the publication of five randomized trials which suggested that platinum based concurrent chemoirradiation should be the first line treatment for carcinoma cervix. They again confirmed the addition of cisplatin showed the superiority of chemo irradiation with an absolute survival benefits of 12 % at the end of 5 years. This has become the basis of widespread practice.[33]

Morris et al in his study confirmed the superiority of chemoirradiation over radiotherapy alone after comparing the 5 year overall and disease free survival.[34]

A Canadian meta-analysis based on 8 randomized studies that evaluated the role of concurrent cisplatin demonstrated a statistical significance in favor of cisplatin with a reduction in the overall relative risk ranging from 30 to 50 % across all stages.[35]

The meta-analysis done by Green et al based on the Cochrane data of 19 trials , 12 based on cisplatin chemotherapy, estimated an absolute improvement in overall survival rate of 12 % from 40 % to 52 % with a 29% reduction in the risk of death. There was an absolute improvement in the progression free survival of 13 % from 47 % to 63 %. There was clear decrease in the local recurrence rate and the distant recurrence rate with chemoirradiation.[36]

3.9 Trials with radiotherapy and concurrent chemotherapy

It has been proved by Sood et al that, concomitant chemotherapy with pelvic irradiation has improved survival among patients with locally advanced carcinoma of the cervix. Each patient underwent two applications of high-dose-rate brachytherapy, 1 week apart. An important issue was the toxicity of concomitant chemotherapy. A retrospective analysis of radiotherapy and high-dose-rate brachytherapy with or without concomitant chemotherapy showed that most patients (93%) who received chemotherapy suffered from acute toxicity, including hematologic toxicity, gastrointestinal toxicity, and deep venous thrombosis. The actuarial incidence of late toxicity was 6%.[37]

Souhami et al did a study to assess the toxicity of the concomitant use of weekly cisplatin and pelvic radiotherapy in patients with locally advanced carcinoma of the cervix with Cisplatin 30 mg/m2. It was found to be well tolerated. No patient required an interruption in the radiotherapy. However, late gastrointestinal toxicity appeared sooner than expected, at a median follow-up time of 11 months after completion of treatment. [38]

3.10 Trials with brachytherapy

When High-dose-rate brachytherapy was introduced in the treatment of cervical cancers, one of the concerns was about the toxicity. A retrospective analysis done by Macleod et al reported a severe late toxicity rate of 4.9%. These results were similar to other reported international studies that have used either low-dose-rate or high-dose- rate brachytherapy.[39]

Various other more aggressive treatment schedules have been practiced elsewhere with HDR brachytherapy. Yoon et al gave a daily fraction dose of 1.8 Gy administered in six-weekly

fractions, from Monday to Saturday. HDR brachytherapy was also delivered in six fractions twice a week. Grade 2 and 3 late rectal complications were encountered in 6.5% and 2.2%, respectively. There were no Grade 3 late bladder complications. They concluded that Six fractions per week of external beam radiotherapy and HDR brachytherapy is effective treatment which therefore can be used for patients with carcinoma of the uterine cervix who cannot be treated with concomitant chemo radiotherapy, like the elderly, or those with multiple medical co-morbidity.[40]

Takeshi et al also found comparable toxicity. External beam radiotherapy and intracavitary brachytherapy using a high-dose-rate 60Co source was used. The 5-year incidence was 2.6% for major bladder complication and 8.3% for major rectal complication. They observed that the higher radiation dose was given in those patients having rectal complication. He also recommended that high-risk patients should be treated with concurrent, chemotherapy.[41]

Other types of application also has shown similar results. A single line source brachytherapy technique was used at Clatterbridge to boost the dose to the primary tumor after external beam radiotherapy (EBRT) for the radical treatment of carcinoma of the cervix. Radiotherapy alone was used. The actuarial rate of Grade 2 late radiation morbidity was 2.7% and 4.3% for the urinary tract and bowel respectively while that of Grade 3 morbidity was only 0.6% and 1.4%, respectively.[42]

Studies by Khoo Tan et al using initially external beam therapy followed by high dose rate brachytherapy also got low complication rate. It reported a serious complication rate of 1.7% only.[43]

3.11 High dose rate brachytherapy fractionation schedules

There were multiple trials in which HDR brachytherapy was fractionated, some interdigitated with the external radiotherapy. They have followed various protocols and the following studies were considered before finalizing our protocol.

Author & Reference	Number	Concurrent Chemotherapy	Fractionation	Toxicity (%)	Outcome	Overall treament time(days).
Yukihiro Hama, et..al..Radiology. 2001;219:207-212.	74	Nil	7Gy x 3# once weekly	32	os-65 dfs-69	(51)
	50	Nil	4.5Gy x 6# twice weekly	6	os-65 dfs-90	(48)
Huh SJ et..al.. *J Korean Soc Ther Radiol Oncol*. 2002 Sep;20(3):237-245. Korean.	106	Nil	24 to 28Gy in 6 or 7 # twice weekly	13	os-73dfs-69 pcr-79	44 to 104 (55)
Shang-Wen Chen et..al..Radiotherapy and Oncology 67 (2003) 69–76	257	Nil (45 adjuv)	7.2Gy x 3# once weekly	rect-25 bow-6 bld-3	*	47 to 92 (63)
	257	Nil	6Gy x 4# once weekly	rect-25 bow-6 bld-3	*	47 to 92 (63)
Robson Ferrigno et..al..Int. J. Radiation Onco Biol. Phys., Vol. 50, No. 5, pp. 1123–1135, 2001	138	Nil	6Gy x 4# once weekly	rect-16 bow-14 bld-11	os-57 dfs-52 pcr-62	39 to 193(60)
Prasert Lertsanguansinchai et..al..Int. J. Radiation Onco Biol. Phys., Vol. 59, No. 5, pp. 1424–1431, 2004	112	Nil	7.5Gy x 3# once weekly	rect-19 bow-3 bld-15	os-69 dfs-70 pcr-87	<49
	112	Nil	8.3Gy x 2# once weekly	rect-19 bow-3 bld-15	os-69 dfs-70 pcr-87	<49
Firuza D Patel et..al..Int. J. Radiation Onco Biol. Phys., Vol. 62, No. 1, pp. 125–130, 2005	113(18)	Nil	9Gy x 5# once weekly	3	os-62 pcr-74	<42

Os	less than 63 days	more or equal to 63 days
Ib/IIa	97	79
IIb	75	72
III	66	49
Pcr		
Ib/IIa	100	87
IIb	93	87
III	83	72

3.11.1 Trials with HDR brachytherapy after external radiation

Yukiro Hama et al recommended that The twice-weekly HDR regimen may improve the local control rate with fewer complications than once weekly regime. He conducted a study with two different fractionation schedules of HDR brachytherapy after external radiotherapy in which 74 patients were treated with weekly once fractionation of 7Gy for 3 applications. The overall treatment time was reduced to 51 days and acute toxicity was reported as 32 percent. He also treated 50 patients with 4.5Gy weekly twice fractionation for 6 applications. The overall treatment time was reduced to 48 days and acute toxicity was only 6 percent.[44]

Huh SJ et al concluded that 24-28Gy in 6 0r 7 applications with twice weekly fractionation is a safe and effective treatment for patients with uterine cervix cancer. He also found out that OTT of less than 55 days had a positive impact on pelvic control and survival rate.

He conducted a study on 106 patients who had radiotherapy with radical intent. The median age was 61 years. He gave 30.6 to 50.4 Gy external beam radiotherapy to whole pelvis with brachytherapy dose of 24~28 Gy in 6~7 fractions to point A at two fractions per week. The median range of overall treatment time was 55 days and toxicity was 13 percent rectal bleeding, which occurred around 13 months after the completion of radiotherapy. The overall survival rate was found to be 82%, and 73%, and the disease free survival rate was 72%, and 69%, with a pelvic control rate of 79% at 3, and 5 years, respectively.

Shang-wen Chen et al recommended to consider changing brachytherapy strategy such that the treatment duration is shortened. He found that the risk of major late complications was not significantly associated with treatment duration. He did a two arm study on 257 patients in which HDR brachytherapy was administered after the completion of external radiotherapy. 93 patients had dose modification to point A to 5 Gy who were treated with an initial calculated rectal dose

of over 6.0 Gy One arm received 7.2Gy weekly once fractionation for 3 applications and the other arm was 6Gy weekly once fractionation for four applications. He reported median overall treatment time of 63 days with the acute toxicity in rectum 25%, bladder 3%, bowel 6%.[45]

3.11.2 Trials with HDR brachytherapy interdigitating with external radiotherapy.

Robson et al suggested that 45 Gy to the whole pelvis combined with four fractions of 6 Gy to point A with HDR brachytherapy is an effective and safe fractionation schedule in the treatment of Stages II and III cervix cancer if realized up to 50 days. He did a study on 138 patients. They were treated with a dose of 45 Gy in 25 daily fractions of 1.8 Gy in 5 weeks. Parametrial boost was performed in 128 patients (93%) with gross parametrial invasion by placement of a 4-cm rectangular midline shielding of 5 Half Value Layers at anterior and posterior

fields. All patients were evaluated after the second week of pelvic external radiotherapy for intracavitary brachytherapy. Whenever possible, HDR was performed during the external radiotherapy course. In cases of unsuitable conditions for intracavitary insertion, HDR brachytherapy was performed after completion of external radiotherapy. He gave 6Gy weekly once fractionation for 4 applications and had median overall treatment time of 60 days with the acute toxicity in rectum 16%, bladder 11%, bowel 14%.[46]

Prasert et al found that there was comparable outcomes between between LDR and HDR intracavitary brachytherapy. He recommended that due to patient convenience, the lower number of medical personel needed, and decreased radiation to health care workers, HDR intracavitary brachytherapy is an good alternative to conventional LDR brachytherapy. In his study

multiple fractions of brachytherapy were integrated with external radiotherapy. Thus the entire treatment was completed within 7 weeks. The external radiothererapy dose per fraction was 2 Gy in all patients. After a dose of 40–50 Gy to the whole pelvis, the patients were evaluated for intracavitary brachytherapy insertion. Brachytherapy insertions were performed weekly and combined with external radiotherapy (with central shielding) by giving four fractions of teletherapy weekly with one brachyhtherapy per week. The dose schedules and fraction of brachytherapy depended on the dose at point A already delivered before central shielding. The shielding of the central structures are done as they receive high doses from brachytherapy.After central shielding, additional external radiotherapy to the pelvic lymph node and parametrium was given to 50–54 Gy. His study was done on 112 patients. One group received 7.5Gy weekly once fractionation for 3 applications and the other group received 8.3Gy weekly once fractionation for 2 applications. The overall treatment time was restricted within 49 days and the acute toxicity in rectum 19%, bladder 15%, bowel 3%.[47]

Firuza D patel et al proved that HDR brachytherapy at 9 Gy/fraction is both safe and effective in the management of carcinoma of the cervix, with good local control and a minimum of normal tissue toxicity . These patients underwent simultaneous external radiotherapy and HDR brachytherapy. External radiotherapy was given to the pelvis with central shielding throughout treatment to a dose of 40 Gy in 20 fractions within 4–5 weeks. Intracavitary brachytherapy

was interdigitated with external radiation. Weekly sessions of 9 Gy of HDR brachytherapy were given from the start of treatment for a total of five sessions. Patients did not undergo external radiation on the day of brachytherapy. She had two groups of patients, Group 1 patients had a 4-cm-wide central block used throughout the externa radiation to shield the central structures

The Group 2 had Stage IIb–IIIb disease with a tumor size _4 cm and distorted cervical anatomy. They underwent external radiotherapy to the whole pelvis to a dose of 46 Gy in 23 fractions within 4.5–5 weeks followed by two appliacations of intracavitary brachytherapy

of 9 Gy each, given 1 week apart. Whole pelvis irradiation was delivered with a dose of 200 cGy/fraction five fractions weekly.

Modification of the treatment plan was required for 4 patients with a rectal dose of _80% of the dose to point A The overall treatment time was less than 42 days and acute toxicity of 3% was reported. So she proved that high dose rate of 9 Gy is well tolerated in Indians.[48]

MATERIALS AND METHODS

IV MATERIALS AND METHODS

Methodology

All patients who have come to the Department of Radiotherapy with biopsy proven carcinoma cervix were considered for the participation in the trial. They were enrolled after signing the informed consent.

4.1 Inclusion Criteria

The patients were screened for the following inclusion criteria and then enrolled.

1. Carcinoma cervix stage IIA to IIIB with Histological confirmation (squamous cell, adenocarcinoma, and adenosquamous carcinoma)
2. ECOG Performance Status score 0-2
3. Adequate bone marrow function: White Blood Cells > 3000/mm3 *(ANC ≥ 1800/mm3);* platelets > 100,000 mm3;
4. Adequate renal function: Creatinine < 1.5 mg/dl *(urinary diversion is permitted to improve renal function)*; patients must have Bilirubin < 1.5 mg/dl, ALT / AST ≤ 2 x normal Alkaline phosphatase. Should give an informed consent prior to participation in study.
5. People of child bearing potential should be willing to practice contraception.
6. Patients responding to radiation therapy and subsequently treated with brachytherapy, were included for analysis.

4.2 Exclusion Criteria

1. Previous history of tumor-directed surgery

2. Previous history of systemic chemotherapy
3. Previous history of pelvic radiation therapy
4. Pregnancy
5. Presence of Metastatic disease
6. Severe co morbid medical condition

Patients who did not respond to radiation therapy and therefore subsequently could not be treated with brachytherapy were not considered for analysis.

4.3 Patient workup scheme and recruitment:

The patients who fulfilled the inclusion and the exclusion criteria were selected for the study. The history and clinical examination findings were reviewed and the lab investigations were followed up. All suitable subjects were explained about the study, and were provided with the literature regarding the study. After reading it and the clarification of any doubts, they were enrolled into the study after obtaining their written informed consent before starting the treatment.

4.4 Pre Treatment evaluation:

After obtaining a detailed history all patients are subjected to a thorough clinical examination. A cervical biopsy was done to confirm the diagnosis.

Blood tests-- Biochemistry-- Renal Function Tests / Liver Function Tests

--Pathology--Complete Blood Counts

-- Virology --Blood Borne Viruses.

Urine analysis--Microscopy / Culture / Pregnancy tests where indicated

Cystoscopy and Proctoscopy.

Radiological tests--Chest X-ray *(PA),* Ultrasonogram abdomen and pelvis (or CT scan).

Baseline ECG.

4.5 Treatment simulation

All patients underwent treatment simulation, prior to initiation of radiotherapy. The treatment portals were marked over the patient and if necessary, the field centers were tattooed. Check films were taken for record. A cross sectional contour of the patient at the treatment centre was taken and tumor volume was drawn. Then it is transferred onto the treatment planning system for finalizing the beams, wedges and the doses.

4.6 External Beam Radiotherapy

Radiotherapy was delivered using Co 60- Theratron 780C machine or the Linear Accelerator. The Anterior pelvic field extended from L4/L5 space to the lowest level of the disease with 2 cm margins and laterally 1.5 to 2 cm beyond the lateral margin of the bony pelvic wall. The anterior border of the lateral fields was kept 3 cm in front of the anterior surface of the L4 vertebral body and posterior at the S2/S3 junction or the sacral hollow was included if required. The upper and lower borders were same as the upper and the lower border of the anterior field. Modification was made for inclusion of nodes or gross tumor as necessary. Total dose of 50 – 50.4 Gy to target volume was given by four field box technique in 25-28 fractions for 5 days in a week (except on those days when brachytherapy was applied) over a period of 5 to 51/2 weeks.

4.7 Concurrent chemotherapy

All patients were planned for concurrent chemo radiotherapy with Cisplatin 40 mg per square meter weekly infusion after checking that the blood tests were within normal limits and after ruling out infection. Cisplatin was given with short hydration and Inj. Dexamethasone 4mg and Inj. Ranitidine 50 mg along with Inj. Ondansetron 8mg as premedication. Following chemotherapy they received Dexamethasone, Ranitidine and Odansetron orally for the next 3 days.

The first cycle of Chemotherapy was given on the day of initiation of radiotherapy. It was given once a week during radiotherapy with a gap of 7 days from the previous date of chemotherapy. The chemotherapy was administered 1 hour prior to radiotherapy in the day care centre. Chemotherapy was continued if there was normal blood counts and creatinine along with normal creatinine clearance. If the creatinine clearance was below 40 then chemotherapy was omitted. If the creatinine clearance was between 40 – 50, 50 % of the calculated dose was given, if 50 - 60 then 75 % of the calculated dose was given and full dose if clearance was above 60. The modified dose of Cisplatin was given as per recommendation of the Avon, Somerset and Wiltshire Cancer Services(ASWCS) cisplatin protocol. Total WBC should be > 4000/mm3 *(ANC ≥ 1800/mm3);* platelets > 100,000 mm3;patients must have, ALT / AST ≤ 2 x normal range, normal Alkaline phosphatase. One patient had received 45 mg weekly, 2 patients 50 mg and while 4 of them received 55 mg and 6 of them had 60 mg weekly cisplatin. One patient had to receive dose modification due to persistent low creatinine clearance.

The following chemotherapy schedule with short hydration was followed in the administration of the concurrent chemotherapy.

RADIOTHERAPY DEPARTMENT

CHRISTIAN MEDICAL COLLEGE AND HOSPITAL, VELLORE.

CHEMOTHERAPY INSTRUCTION SHEET

Name: H. No.

HEIGHT WEIGHT BSA

Name of drug	Dose	Route	Days
Inj. Cisplatin*	(40 mg/m2) IV in 1 pint normal saline over 1 hour with hydration* and premedication**	weekly	

1. Repeat the course after _7__ days from Day _1__
2. The following investigations must be done before chemo.

Investigation(s)	
Hb, Platelet, WBC}	before each course
S.Creat }	before each course
LFT }	before each course

4. If the serum creat or LFT is abnormal, if the WBC falls below 4000/cumm platelet below 100,000/cumm and Hb below 8gm and if toxic symptoms like severe vomiting, diarrhoea, fall of BP and mucositis of buccal mucosa develop, the drugs are to be discontinued. After a period of 4 to 5 days if the counts regain normal values, the drugs may be continued as instructed after careful re-evaluation of the patient's condition.

*HYDRATION SCHEDULE TO BE FOLLOWED FOR INJ. CISPLATIN:

Inj. Dextrose Normal saline 1000 ml over 2 hours
Inj. Mannitol 12.5% 100ml over 1/2 hour

Premedication

Inj. Cisplatin in 300 ml Normal saline over 1 hour

Inj. Dextrose Normal saline 500 ml over 1 hour

**ANTIEMETIC REGIME FOR CISPLATIN BASED CHEMOTHERAPY.

1.Inj. Dexamethasone 8 mg IV stat before cisplatin
2.Inj. Ondansetron 8 mg IV stat before cisplatin.
3.Inj. Ranitidine 50 mg IV stat before cisplatin
4.Inj. Ondansetron 8 mg IV after 6 hours after cisplatin

Post chemotherapy antiemetic regimen:

1. Tab. Dexamethasone 4 mg twice daily X 3 days
2. Tab. Ranitidine 150 mg twice daily X 3 days.
3. Tab. Lorazepam 1 - 3 mg at bed time.
4. Tab. Emeset 8 mg as necessary for nausea.

4.8 Intracavitary brachytherapy

The patient was admitted in the ward one day prior to the procedure. All patients had soap water enema for bowel preparation and vaginal douche prior to the intracavitary applicator placement. The patient was on soft diet.

PROCEDURE

After positioning the patient in the lithotomy position the perineum was cleaned using Betadine solution. The bladder was initially emptied using a metal catheter and then catheterized using 16 Fr Foleys catheter and the bladder bulb was inflated with 7 ml of contrast plus saline (2ml contrast and 5ml saline). The cervical os was identified and the uterus was sounded. It was progressively dilated. The central tandem was first introduced followed by the two ovoid tandems. The vaginal packing was done initially posteriorly with the packing gauze soaked in contrast. The rest of the vagina was then packed with the same gauze which was soaked with betadine. After a satisfactory packing, a rectal marker was inserted for at least 10 cm into the rectal lumen. HDR brachytherapy was performed using HDR Nucletron Micro Selectron brachytherapy unit using 192Ir source as remote after loading technique. Orthogonal AP and

lateral films were taken on the simulator with dummy sources and radiopaque markers to identify the bladder and rectum. Simulation films were taken for all patients, and the dose was calculated on the treatment planning system.

4.9 Prescription

A dose of 7.2 Gy to point A weekly once fractionation using HDR brachytherapy. It was scheduled with a gap of 7 days from the previous brachytherapy or the last chemotherapy, after assessment of toxicity. It was applied weekly once for a period of 3 weeks.

Dosimetry

For patients treated using four field techniques, the dose distribution was done using the Plato treatment planning system. HDR brachytherapy dosimetry was calculated on the Plato treatment planning system using orthogonal films for each insertion. The rectal and bladder reference dose points were determined according to the International Commission of Radiation Units and Measurement Report 38, guidelines for rectal doses (ICRU rectal point). The dose at point A, the rectal reference point, bladder reference dose, and isodose distributions were calculated using computer-based software (Nucletron Plato System PSS, Version 3.7.7).

4.10 Planned Treatment Schedule

Week	Day	Radiation	Chemotherapy
1	1	External RT	Concurrent Cisplatin 40 mg/m^2 after assessment
	2	External RT	
	3	External RT	
	4	External RT	
	5	External RT	
	6, 7	---	
2	8	External RT	Concurrent Cisplatin 40 mg/m^2 after assessment
	9	External RT	
	10	External RT	
	11	External RT	
	12	External RT	
	13,14	---	
3	15	External RT	Concurrent Cisplatin 40 mg/m^2 after assessment
	16	External RT	
	17	External RT	
	18	External RT	
	19	External RT	
	20,21	---	
4	22	External RT	Concurrent Cisplatin 40 mg/m^2 after assessment
	23	External RT	
	24	External RT	
	25	External RT	
	26	External RT	
	27,28	---	
5	29	Brachytherapy	Assessment Under Anesthesia
	30	External RT	
	31	External RT	
	32	External RT	
	33	External RT	
	34,35	---	
6	36	Brachytherapy	Assessment Under Anesthesia
	37	External RT	
	38 – 42		
7	43	Brachytherapy	Assessment Under Anesthesia
	44 -49		
8	50		

Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Publish Date: December 12, 2003

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
DERMATITIS	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site
VAGINAL DRYNESS	Mild	Interfering with sexual function; dyspareunia;	---	---
VAGINAL MUCOSITIS	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
PROCTITIS	Minimal discomfort, intervention not indicated. Erythema of the mucosa	Symptomatic, medical intervention indicated but not interfering with ADL; Patchy ulcerations or Pseudomembranes	Stool incontinence or other symptoms interfering with ADL Confluent ulcerations or pseudo membranes;bleeding with minor trauma	Symptom associated with life threatening consequences Tissue necrosis;significant spontaneous bleeding; life threatening consequences
CYSTITIS	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated
BLADDER SPASMS	Symptomatic, no intervention	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated
ENTERITIS	Asymptomatic,pathol ogic or radiographic findings Only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever,change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (perforation, bleeding,ischemia, necrosis)
DIARRHOEA	Increase of <4 stools per day over base line; mild increase in ostomy output compared to base line	Increase of 4 – 6 stools per day over base line; IV fluids indicated <24hrs; moderate increase in ostomy output compared to base line; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24hrs hospitalization, increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)
ABDOMINAL PAIN	Mild pain not interfering with function	Moderate pain; pain interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling
NEURO TOXICITY	Asymptomatic, weakness on exam/testing only Asymptomatic; loss of deep tendon reflexes or	Symptomatic weakness interfering with function, but not interfering with ADL. Sensory alteration or paresthesia (including tingling)	Weakness interfering with ADL; bracing or assistance to walk (e.g.,cane or walker) indicated Sensory alteration or paresthesia interfering with ADL	Life-threatening; disabling (e.g., paralysis)
ALLERGY	Transient flushing or rash; drug fever <38°C (<100.4 F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema / angio edema; hypotension	Anaphylaxis
EMESIS	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, indicated ≥24 hrs	Life-threatening Consequences
NAUSEA	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences

FEBRILE NEUTROPENIA (fever of unknown origin without clinically or micro biologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	----	----	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection).				
INFECTION (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L)		Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)
Infection with normal ANC or Grade 1 or 2 Neutrophils		Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; operative intervention indicated	Life-threatening consequences (septic shock, hypotension, acidosis, necrosis)
Infection with unknown ANC		Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)
Alopecia	Thinning or patchy	Complete		
Fever(F)	100.4 to 102.2	102.3 to 104.0	104.0 for <= 24 hours	104.0 for > 24 hours
Fatigue	Mild	Moderate, causing difficulty performing some ADL	Severe, interfering with ADL	Disabling
Insomnia	Occasional difficulty sleeping	Difficulty sleeping interfering with function	Frequent difficulty sleeping interfering with ADL	Disabling

4.11 Assessment of toxicity

All patients were assessed for toxicity every week as per the planned schedule using RTOG / CTCAE version 3.0 assessment tool. They were examined and their symptoms noted. They were carefully examined for a any radiation induced or chemotherapy causing toxicity which were then documented. The blood tests done were reviewed and then decided whether to proceed with chemotherapy. If there was any Grade III and above toxicity as per the assessment, then chemotherapy and radiation was deferred and appropriate treatment initiated. The response to the treatment started were closely monitored.

4.12 Assessment for brachytherapy

At 36 Gy the patients were assessed for the feasibility of interdigitating brachytherapy. If the tumor response was adequate and intracavitary feasible the first fraction of brachytherapy was given at 40 Gy followed by weekly once fraction for three weeks. If the tumor response is not adequate, reassessment was done again after one week for the feasibility of application of brachytherapy. If there was still an inadequate response of the tumor and brachytherapy not feasible then external radiotherapy was continued with smaller fields till completion.

Treatment time: Overall treatment time (OTT) was taken from the first day of external radiotherapy to the last day of brachytherapy. The reasons for treatment delay were noted.

4.13 First follow up evaluation

The first follow up was done after 6 weeks. History of all the complaints and a thorough clinical examination is done. The clinical evaluation was done to assess the tumor response as well as any toxicity.

4.14 Statistical Analysis

A descriptive analysis and frequency distribution of the patient characteristics was done. Frequency distribution was done to assess the toxicities. Anova and Chi –Square tests was done to see if there was any associated factor which can be related to inadequate tumor response to the treatment given.

Ethical Consideration

The institutional Review Board (IRB) had considered the study in its ethics committee and cleared the same before the study was started.

RESULTS

V RESULTS

From the month of May 2009 to November 2009, 72 patients were newly registered with the diagnosis of carcinoma cervix. Some were referred cases, some were treated elsewhere and come for follow up and some came only for evaluation and confirmation of diagnosis.

Among these patients 39 were evaluated for treatment and screened for eligibility to be included in the study out of which 27 patients were enrolled after their informed consent.

Four of these patients have not completed the therapy therefore not included in the analysis. Following enrollment 4 patients withdrew from the study; another 2 defaulted while 1 patient was a screen failure.

5.1 Patient turnout

16 patients completed their treatment by the end of November out of which 3 patients did not undergo brachytherapy due to inadequate response and therefore were not fit for brachytherapy. Out of the remaining 13 patients, 8 patients could undergo brachytherapy interdigitating with external radiotherapy while 5 patients could undergo this only after the completion of external radiation therapy.

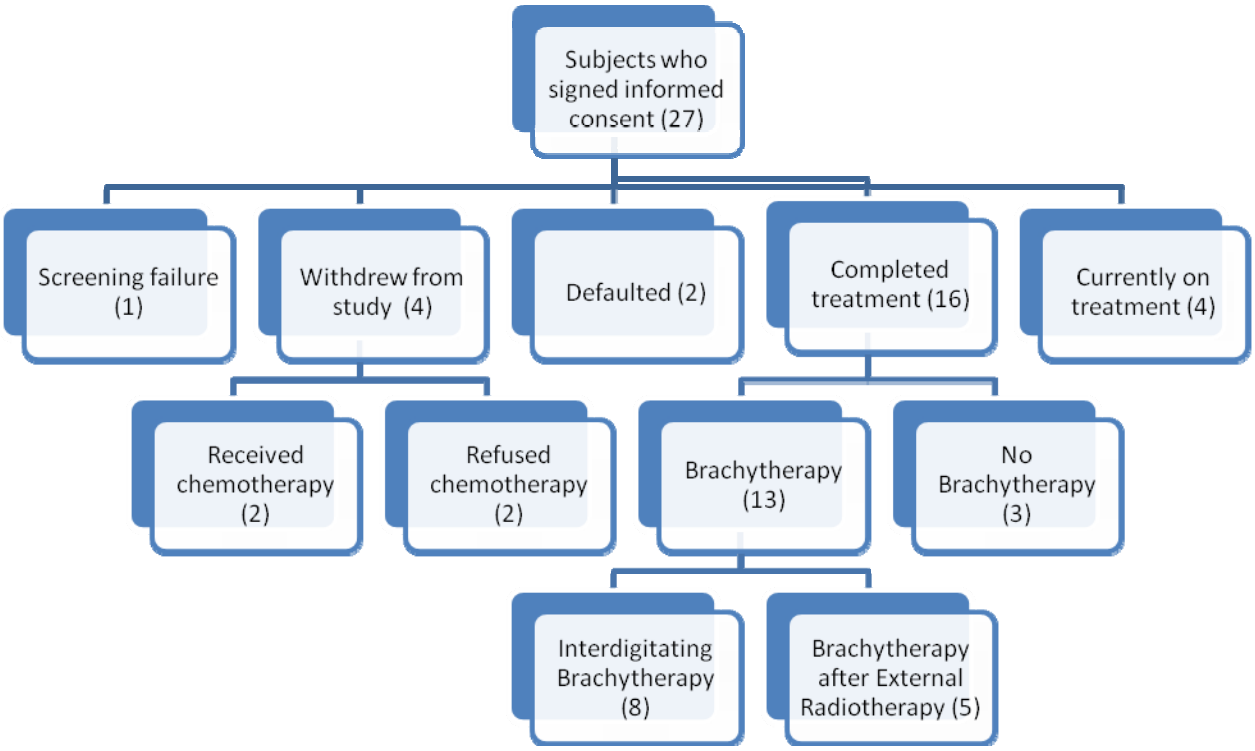


Figure-1: This shows the pictorial representation of the turnouts of all the patients who have signed the consent form.

The following table shows the patient characteristics.

Table-1: Patient Characteristics-History

Age	Occup	BPV	PCB	WDPV	Abd pain	Back pain	Mar/ Wid	Pre/ Meno	Gra	Par	Liv	Abo	Diseases
48	TEACH	180	0	30	0	0	Married	Pre	3	3	3	0	
52	HWIFE	30	0	365	0	0	Married	Meno	6	6	5	0	
45	HWIFE	150	150	60	0	0	Married	Meno	3	3	3	0	
43	HWIFE	180	360	180	0	0	Married	Meno	4	4	4	0	
48	TEACH	180	0	0	0	30	Married	Pre	3	3	3	0	
59	HWIFE	90	0	0	0	0	Widow	Meno	6	6	6	0	HT,EPILEPSY
52	HWIFE	60	0	0	60	60	Married	Pre	3	2	2	1	RHEU ARTH
48	HWIFE	150	0	150	30	150	Married	Pre	2	2	2	0	
47	HWIFE	240	1	120	0	0	Married	Meno	5	5	3	0	
41	HWIFE	120	30	120	0	0	Married	Pre	2	2	2	0	
38	HWIFE	60	0	0	0	0	Married	Pre	5	4	3	1	
30	HWIFE	90	0	0	90	0	Married	Pre	1	1	1	0	
35	HWIFE	0	15	0	0	0	Married	Meno	4	3	2	1	OTOSCLER

Legend
Age in years, Occup-Occupation: House wife/ Teacher , BPV- Bleeding Per Vaginum in days , PCB- Post Coital Bleeding in days , WDPV-White Discharge Per Vaginum in days , Abdominal Pain in days , Back pain in days , Marital status: Married / Widowed , Menstrual Status: Menopausal/ Pre-menopausal , Gra-Gravida ,
Par-Parity, Liv-Live, Abo-Abortion, HT- Hypertension, RHUE ARTH- Rheumatoid Arthritis, OTOSCLER- Otosclerosis

5.2 Patient characteristics

It can be seen that except for two teachers, all of them were housewife in their occupation. All of them were married and one is a widow. Seven of them were premenopausal women.

5.2.1 History- None of the patients had complaints of dyspareunia, fever, and fatigue at the start of treatment. None of them had any bladder or bowel complaints.

One patient was a hypertensive and also had a history of seizure disorder while another had Rheumatoid Arthritis and the third patient had Otosclerosis. There was no one with the history of Diabetes, Ischemic Heart Disease or Tuberculosis.

Table 2: Description of presenting Complaints

Parameter	Number	Minimum (days)	Maximum (days)	Mean (days)
Bleeding PV	12	30	240	127.50
Post Coital Bleed	5	1	360	111.20
White Discharge PV	7	30	365	146.43
Abdominal pain	3	30	90	60.00
Back Pain	3	30	150	80.00

Except for one patient, all of them presented with bleeding per vaginum. Five of the patients complained of post coital bleeding. Seven of them had white discharge per vaginum. Only three of them complained of lower abdominal pain or low backache.

5.2.2 Examination findings

The general examination showed that all patients had good performance score. None of them had clinically evident pallor. Their systemic examination was within normal limits except for one who had tricuspid regurgitation. None of them had any handicaps or any deformities.

The table below shows the relevant findings in the pelvic examination.

Table 3: Examination findings showing the region involved by the tumor.

Region involved	**Number**
Fornix-Anterior	6
Fornix –Posterior	7
Fornix-Rt Lateral	6
Fornix-Lt Lateral	10
Vagina Upper two thirds	9
Vagina Lower third	0
Parametrium Not up to side walls	11
Parametrium up to side walls	2
Cervix both lips	13
Bladder and Rectum	0

Table 4: Clinical staging

Stage	Frequency	Percent	Cumulative Percent
2B	11	84.6	84.6
3B	2	15.4	100.0
Total	13	100.0	

5.2.3 Clinical stage- Except for 2 of the patients who were stage III B, all of them belonged to stage II B.

5.2.4 Investigation findings

All of the patients had their biopsies reported by the pathologists in CMC as squamous cell carcinoma. Their subtypes are shown as follows:

Table 5: Sub types of Squamous cell carcinoma-histology

Histology	Frequency	Percent	Cumulative Percent
Poorly differentiated	4	30.8	30.8
Moderately differentiated	7	53.8	84.6
Non keratinizing	2	15.4	100.0
Total	13	100.0	

Majority of the patients had moderately differentiated carcinoma, 2 reported as non keratinizing squamous cell carcinoma while 4 had poorly differentiated carcinoma.

Radiological tests with USG and Chest X ray did not reveal any metastatic lesions elsewhere in the body. There were no other abnormalities detected in the lung, liver or kidney.

5.3 Hematological toxicity

Hemoglobin- 3 patients had a drop in Hb while on treatment needing blood transfusion.

Platelets- 3 patients had a drop in platelet count below 0ne lakh while on treatment and it resulted in delay of the overall treatment time.

LFT - The liver enzymes were found to be normal throughout the treatment.

Creatinine clearance dropped below 50 in two patients needing a delay in the treatment with chemotherapy. One patient had persistently low creatinine clearance and chemotherapy was given with dose modification as per Avon, Somerset and Wiltshire Cancer Services (ASWCS) guideline.

Table 6: Neutropenia

Absolute Neutrophil Count	Number of patients
Grade III	3
Grade IV	4

Absolute Neutrophil Count- Seven patients had a significant reduction in neutrophil counts. Three patients developed Grade III toxicity and four developed Grade IV toxicity. This was one of the important factors causing the delay in overall treatment time.

5.4 Gastrointestinal toxicity

Table 7: Complaint of nausea

Nausea	Number of patients	Frequency	Percent	Cumulative percent
Absent	5	62	73.81	73.81
Grade 1	7	21	25	98.81
Grade 2	1	1	1.19	100

Eight patients had complaints of nausea out of the 13 after treatment with radiation and chemotherapy. There were 22 episodes of complaints of nausea. However there were only 3 episodes of complaints of vomiting.

Table 8: Incidence of diarrhea and abdominal pain

Diarrhea	Number of patients	Frequency	Percent	Cumulative percent
Absent	6	73	61.32	61.32
Grade 1	4	8	7.67	68.99
Grade 2	3	3	2.56	100
Abdominal pain	Number of patients	Frequency	Percent	Cumulative percent
Absent	6	71	84.52	84.52
Grade 1	7	13	15.48	100

Seven patients had diarrhea and 7 had abdominal pain. Occurrence of loose stools was one of the factor to cause a delay in the treatment plan causing a lengthening in the overall treatment time for one patient.

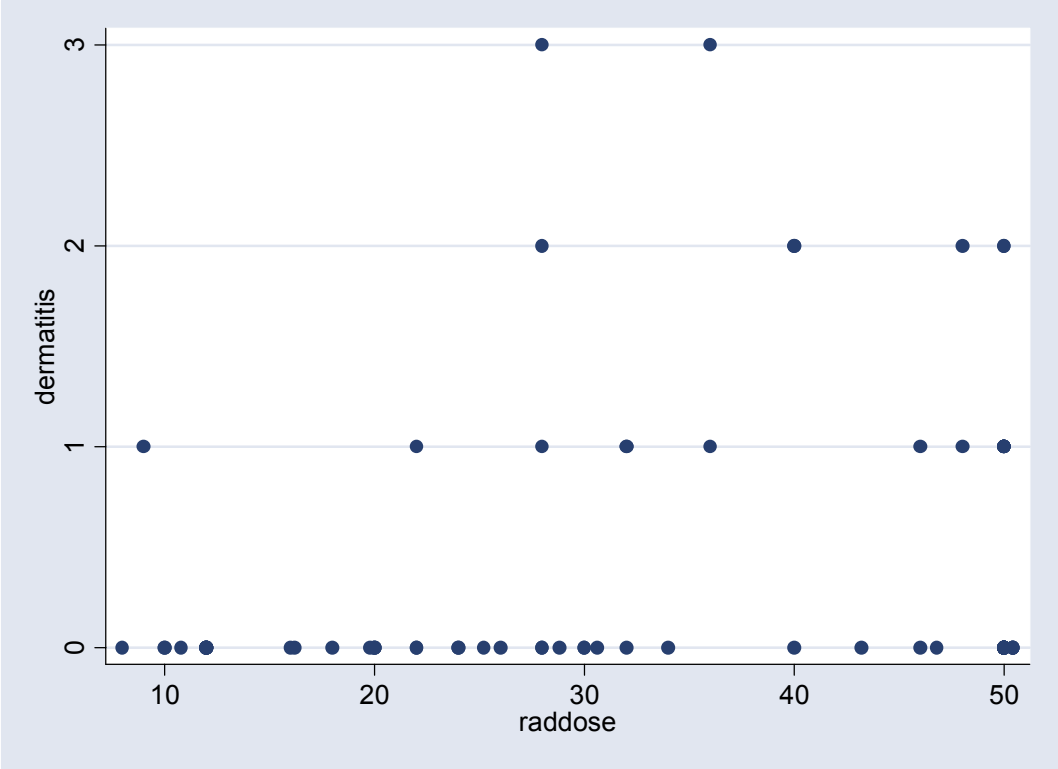
5.5 Non hematological toxicity

Table 9: Occurrence of Vaginal mucositis and dermatitis.

Vaginal mucositis	Number of patients	Frequency	Percent	Cumulative percent
Absent	3	67	75.28	75.28
Grade 1	5	14	15.73	91.01
Grade 2	1	2	2.25	93.26
Grade 3	4	6	6.74	100
Dermatitis	Number of patients	Frequency	Percent	Cumulative percent
Absent	3	59	66.29	66.29
Grade 1	4	17	19.1	85.39
Grade 2	2	7	7.87	93.26
Grade 3	4	6	6.74	100

Delay of the completion of the treatment occurred due to grade 3 radiation dermatitis and vaginal mucositis. Grade III reaction occurred in 4 patients needing a break in the treatment. There were 6 episodes of grade 3 and 24 episodes of Grade I and Grade II toxicity.

Below is a distribution of radiation dermatitis and vaginal mucositis with the radiation dose received.



It can be seen that radiation dermatitis and vaginal mucositis is seen to be related to the radiation dose received.

5.6 Other toxicities.

Table 10: Complaints of fatigue and insomnia

Fatigue	Number of patients	Frequency	Percent	Cumulative percent
Absent	4	62	73.81	73.81
Grade 1	9	22	26.19	100

Insomnia	Number of patients	Frequency	Percent	Cumulative percent
Absent	6	68	80.95	80.95
Grade 1	7	16	19.05	100

One complaint which occurred but did not cause a delay in the treatment was fatigue. There were 22 episodes of fatigue.

There was no complaint of allergy, alopecia, neurotoxicity at any given time.

5.7 Treatment delays

Table 11: Reasons for delay in the planned treatment in each week.

Week	Reasons for delay in planned treatment
First	Low platelets
Second	Loose stools, Increasing Creatinine
Third	Loose stools, Urinary Infection, neutropenia, Low Creat clearance,Low platelets
Fourth	Neutropenia, Machine repair, Loose stools, Low platelets, Bleeding PR, Urinary infection, fever, Grade III radiation induced dermatitis and vaginal mucositis
Fifth	Persistent neutropenia, Grade III radiation induced dermatitis and vaginal mucositis reaction in vulva, fever
Sixth and above	Persistent Neutropenia, Low platelets, Grade III radiation induced Vulval Reaction and vaginal mucositis

The reasons for delay in chemotherapy in each week are as follows:

In the first week one patient could not be started on chemotherapy on day 1 due to low platelet.

In the second week 1 patient did not get chemotherapy on time due to the complaint of loose stools associated with increasing creatinine level.

In the third week loose stools were the cause of delay in 3 patients while low counts associated with urinary infection was seen in one patient. Two patients had low platelets and another two patients had low creatinine clearance interfering in the treatment.

In the fourth week, loose stools were seen in 2 patients, decreased counts in one patient. One each had complaints of Grade III radiation induced dermatitis and vaginal mucositis, low platelets, bleeding per rectum, and infection causing the delay. One day delay was caused due to machine repair.

By the fifth week many patients had delay due to multiple reasons. Neutropenia alone was seen in 6 patients, radiation induced dermatitis and vaginal mucositis in 3 patients, one patient had neutropenia with radiation induced dermatitis and vaginal mucositis. One patient had neutropenia with thrombocytopenia. One patient had fever along with low counts. One day delay was found in one patient due to theatre unavailability.

From the sixth week onwards significant delays were caused by persistent neutropenia (one patient), low platelets (one patient), and radiation induced dermatitis and vaginal mucositis(one patient). One day delay was found in one patient due to theatre unavailability.

5.8 Overall treatment time

Table 12: Time for treatment completion and reasons for delay.

8 weeks	9 weeks	➢ 9weeks
4	5	4
Reasons	Neutropenia(3) Grade III RT reaction(2)	Neutropenia(2) Thrombocytopenia(1) Grade III RT reaction(1) Loose stools(1)

Four patients completed their treatment within 8 weeks time, 5 completed in 9 weeks. Of these 5 patients, 3 had prolonged neutropenia while the other 2 had radiation induced dermatitis and vaginal mucositis causing the delay in their completion of their treatment.

Four patients took longer than 9 weeks to complete their treatment due to persistent neutropenia (one patient), thrombocytopenia (one patient), and Grade III radiation induced dermatitis and vaginal mucositis (one patient) and loose stools with neutropenia (one patient).

5.9 Failure to interdigitate brachytherapy

The following are the reasons why brachytherapy could not be interdigitated in 5 patients and brachytherapy application not done in the other 3 patients -

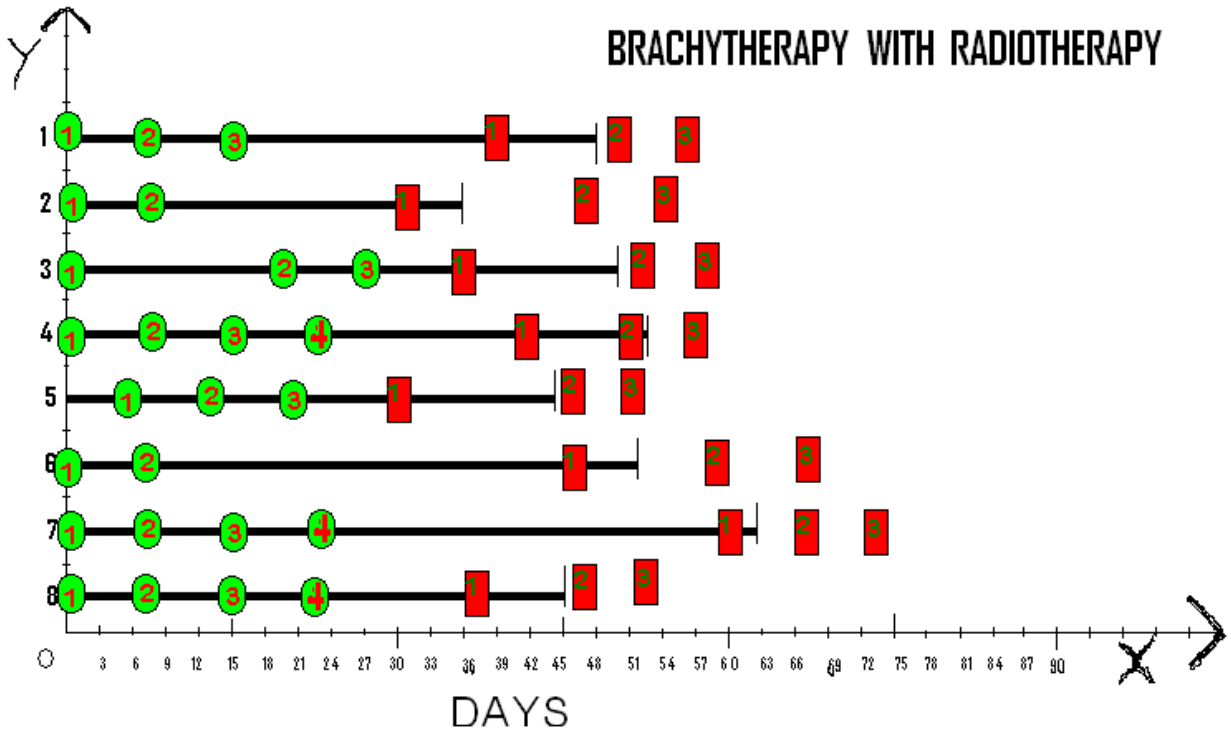
Two patients had Grade III radiation induced dermatitis and vaginal mucositis not allowing brachytherapy application.

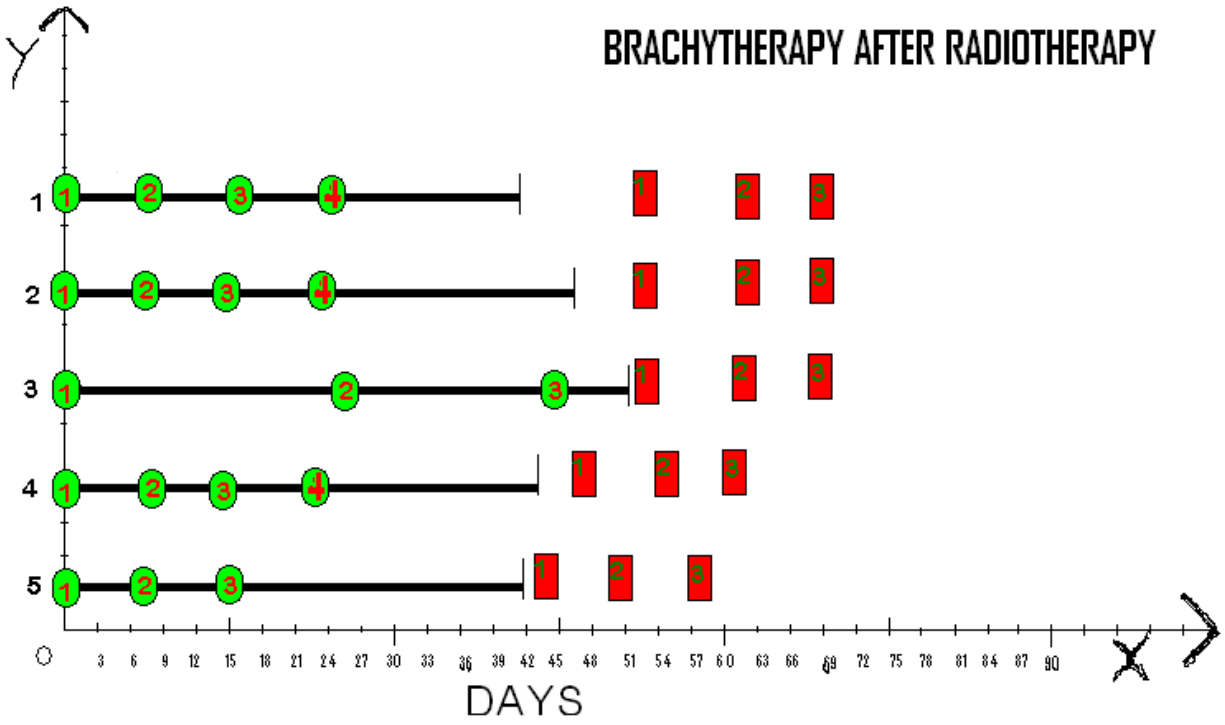
One patient had persistent neutropenia causing the delay in the procedure.

The other 2 patients did not have adequate response to the chemoirradiation already given.

3 patients did not have any brachytherapy at any time due to inadequate response to the radiation even at the end of 50 Gy.

The following is a pictorial representation to show the treatment given.





LEGEND

Period of treatment

--- Fraction of brachytherapy

--- Cycle of chemotherapy

FIGURE 2: This figure is a pictorial representation of the treatment received by the patients. The chemotherapy received and the brachytherapy applications are shown. (Not to scale).

5.10 Treatment response in relation to other parameters

An analysis was done for all 16 patients to see if there is any relation with response to the treatment at 40 Gy as evaluated clinically with other factors.

The following tables show the significance of the relationship between these factors and the response to treatment as clinically assessed at 40 Gy.

Table 13: Multivariate Analysis of Outcome (as assessed clinically- response at 40 Gy) and clinical and biochemical parameters.

PARAMETER	F VALUE	P Value (2 tailed)
HB ANY TIME LESS THAN 10	.017	.898
BASELINE HB	1.007	.333
BASELINE WEIGHT	.021	.886
MAX. LOSS OF WEIGHT	1.523	.239
TECHNIQUE 2D/3D	.884	.363
ANYTIME CREATININE CL. < 55	.131	.723
EVERYTIME CREATININE CL.>60	.131	.723
AGE	.345	.566
HISTOLOGICAL SUB TYPES	.579	.459
NUMBER OF CHEMOTHERAPY	1.916	.188

The factors which were taken into account were baseline Hemoglobin, anytime Hemoglobin less than 10, baseline weight and loss of weight, creatinine clearance less than 55 anytime against always above 60, clinical stage, technique of treatment 2D versus 3D, the age of the patient, the differentiation of the tumors as well as the total number of chemotherapy received.

Table 14: Analysis of Outcome (as assessed clinically- response at 40 Gy) and histological sub type of squamous cell carcinoma.

HISTOLOGY SUB TYPE	RESPONSE		Total
	NO	YES	
Poorly differentiated	1	4	5
Moderately differentiated	3	6	9
Non keratinizing	1	1	2
Total	5	11	16

P VALUE (2 TAILED)= 0.640

5.10.1 Relation to histological Sub type -Analysis was done to see if the response is related to the histological Sub type, whether poorly differentiated is more responsive compared to the well differentiated. There were 5 poorly differentiated type of squamous cell carcinoma and 9 moderately differentiated squamous cell carcinoma. However the test did not show any significance.

Table 15: Analysis of Outcome (as assessed clinically- response at 40 Gy) and technique of radiation conventional (2D) and conformal (3D).

RADIATION TECHNIQUE	RESPONSE		Total
	NO	YES	
conventional(2D)	4	6	10
conformal(3D)	1	5	6
Total	5	11	16

P VALUE (2 TAILED)= .950

5.10.2 Relation to technique of radiation -With the onset of more and more sophistication, and more people affording and opting for the conformal radiation therapy over the conventional form of radiation, an analysis was done to see if the response of the tumor was in any way related to the technique used. There were 10 patients treated with conventional 2D technique and 6 patients treated with conformal 3D technique. It did not show any significance.

Table 16: Analysis of Outcome (as assessed clinically- response at 40 Gy) and number of cycles of chemotherapy received.

NUMBER OF CHEMOTHERAPY	RESPONSE		Total
	NO	YES	
2	0	2	2
3	1	4	5
4	4	5	9
Total	5	11	16

P VALUE (2 TAILED)= 1.933

5.10.3 Relation to number of chemotherapy -Response of the tumor with respect to total number of chemotherapy received by the patient was looked at. Two patients had received 2 cycles of chemotherapy with cisplatin, 5 patients had received three and the remaining 9 had received 4 cycles of chemotherapy respectively. It was analyzed and found that there was no significance seen. A T test was also done. Test of significance was done for factors such as baseline Hemoglobin, anytime Hemoglobin less than 10, baseline weight and loss of weight, creatinine clearance less than 55 anytime against always above 60 and no significant results was found.

DISCUSSION

VI DISCUSSION

Cervical cancer remains a significant health problem for developing countries. Multiple trials have clearly indicated that platinum based concurrent chemoirradiation should be the first line treatment for carcinoma cervix. They again confirmed the addition of cisplatin showed the superiority of chemo irradiation with an absolute survival benefit of 12 % at the end of 5 years.[49] Therefore the standard treatment for carcinoma of cervix stage 2 and 3 is a combination of external beam radiotherapy with once weekly concurrent chemotherapy using Cisplatin and brachytherapy. Usually brachytherapy done in cancer cervix is low-dose-rate (LDR). With the advent of the high-dose-rate brachytherapy, low dose rate brachytherapy has been replaced by the high dose rate brachytherapy (HDR). The potential disadvantages like long treatment time, radiation exposure to the health professionals, hospitalization for therapy, the associated risks of anesthesia, thromboembolism due to prolonged bed immobilization, prolonged discomfort of vaginal packing, potential chance of displacement of the applicators etc were overcome with HDR application.

The members of the American Brachytherapy Society[50] who are experts in HDR cervical brachytherapy recommend HDR brachytherapy over the LDR in cancer of the cervix due to the following advantages.

1. The radiation exposure hazard for caregivers, visitors and other personnel are eliminated while preparing the source and while it is being transported.

2. It reduces the treatment times thereby causing

a) decreased patient discomfort as prolonged bed rest is eliminated.

b) It is possible to treat patients who may not tolerate long periods of isolation and those who are at high risk for deep vein thrombosis.

c) As the patient is more comfortable and more compliant there is lesser risk of applicator movement during therapy.

d) Patients can be treated as Outpatient thereby reducing hospitalization leading to lesser expenses.

e) There is possibility of greater displacement of critical organs either by packing or by using rectal retractor, thereby reducing rectal and bladder morbidity.

f) The number of patients being treated can be increased due to the time saving and other conveniences thereby optimizing the facilities of institutions in some developing countries.

3. It allows the use of smaller diameter sources than those used in LDR:

a) The need for dilatation of the cervix is reduced thereby reducing the need for heavy sedation or general anesthesia.

b) High-risk patients for general anesthesia can now be more safely treated.

c) Easier insertion of applicators into the cervix.

4. Makes dose distribution optimization possible. The variation of dwell time with source allows greater control of the dose distribution and potentially less morbidity.

5. Allows interdigitation of external radiation with brachytherapy which can lead to a shorter overall duration of treatment and potentially better tumor control.

Further; randomized trials by Shigematsu et al and Patel et al have demonstrated that HDR brachytherapy is an equal alternative to conventional low-dose-rate brachytherapy in the treatment of uterine cervical carcinoma.[51] Also a major advantage of HDR brachytherapy is ooptimization of dose distribution with better control of the dose distribution and potentially less morbidity. Occurrence of potential late toxicities that are associated with large dose per fraction is one of the main disadvantages of HDR brachytherapy but this can be overcome with adequate fractionation. Trials have shown that reduced overall treatment time is one of the factors that influences cure of cervical cancer. With HDR brachytherapy interdigitation with external beam radiotherapy is possible which could lead to a shorter overall treatment time and therefore possible better tumour control.

A wide variety of fractionation regimes have been tried with high dose rate brachytherapy to achieve reduced treatment time for the purpose of reducing the mortality. Results of various trials indicate that one practical option which was feasible with high dose rate brachytherapy which was not possible with low dose rate brachytherapy was to interdigitate the brachytherapy along with external radiotherapy. In our study this was done after 4 weeks of external beam radiotherapy with concurrent 4 cycles of weekly regimen of Cisplatin.

No clear consensus of the appropriate number of fractions or the dose per fraction has been reached. Various fractionation schemes have been used experimentally in search of the optimal technique. The American Brachytherapy Society recommends fraction size of _7.5 Gy using four to eight fractions of HDR brachytherapy but recognizes that there is insufficient data to clearly recommend any one regime in favor of others due to lack of experience.[2] In this study 7.2 Gy weekly once regime for 3 weeks was used.

Most of our patients had stage 2b carcinoma cervix with proliferative growths and had good performance status. All of them had squamous cell carcinoma which is the most common type. Their main presenting complaints were bleeding PV, white discharge PV and post coital bleeding. Few of them had backache or abdominal pain. None of them had bleeding severe enough to undergo any blood transfusion or immediate intervention. None of them had any complaints related to bladder or rectum. Among the patients included in the study 6 of them underwent conformal radiation therapy.

Only one patient had hypertension and seizure disorder and another had Rheumatoid Arthritis while the third patient had Otosclerosis. There was no other co morbid systemic illnesses among the remaining patients.

Sood et al have reported that although concomitant chemotherapy with pelvic irradiation has improved survival among patients with locally advanced carcinoma of the cervix, most patients (93%) who received chemotherapy suffered from acute toxicity, including hematologic toxicity, gastrointestinal toxicity and deep venous thrombosis. But the actuarial incidence of late toxicity was however only 6%.[52]

The toxicity due to chemotherapy with radiation were mainly severe neutropenia followed by thrombocytopenia in our patients. About half of our patients developed hematological acute toxicity. Nausea and loose stools were also commonly seen. These toxicities were seen to delay the overall treatment time. A recent meta-analysis on toxicity following radiation alone or in combination with chemotherapy for locally advanced cervical cancer confirmed that concurrent chemotherapy increases acute toxicity – gastrointestinal and hematologic – as compared with radiation alone[53]. The toxicity seen by the time of assessment for brachytherapy was mainly due

to concurrent chemoirradiation. In our study, 3 patients had grade 3 radiation induced dermatitis and vaginal mucositis causing delay in the overall treatment time while another 3 developed grade 3 neutropenia and 4 had grade 4 neutropenia causing a delay. One patient had Urinary infection which required hospitalization and caused a delay in chemotherapy as well as radiation therapy. Acute Gastrointestinal toxicity was common though not severe enough to cause major interruptions in the treatment in all our patients except one. However late effects of chemoirradiation needs to be carefully monitored as suggested in literature[54].

Overall, 6 patients had completed 4 cycles of chemotherapy, the others could not due to hematologic or renal toxicity. All of them except two received at least three cycles.

Although there is literature reporting the use of 6 cycles of concurrent chemotherapy along with radiation therapy[55], we have used only four cycles in our study because of the problems of low blood counts, and potential delay in brachytherapy if more number of chemotherapy is given.

The overall treatment time was seen to range from 51 days to 77 days. 4 patients completed within 8 weeks and another 5 within 9 weeks. The other 4 patients took more than 9 weeks to complete the treatment due to persisting neutropenia, thrombocytopenia and radiation induced dermatitis and vaginal mucositis. One of them had loose stools causing the delay.

The response to treatment was assessed clinically at the end of 40 Gy with a view of consideration for the application of brachytherapy. It was seen that response was more in the poorly differentiated than in the moderately differentiated tumors even though it was not found to be statistically significant. It was also seen that the response among the conformal group was more when compared to the conventional technique of radiation. There was no apparent benefit seen in response due to the increased number of chemotherapy received. However all these

parameters when checked for any statistically significance did not reveal any significant difference.

Analysis done to see if there is any relation with response to the treatment at 40 Gy as evaluated clinically with factors like baseline Hemoglobin, anytime Hemoglobin less than 10, baseline weight and maximum loss of weight, creatinine clearance less than 55 anytime against always above 60, clinical stage, technique of treatment 2D versus 3D, the age of the patient, the differentiation of the tumors as well as the total number of chemotherapy received did not show any significant result. The reason a difference was not seen may be due to the less number of patients in the study.

Among the 16 patients for 3 patients brachytherapy was not feasible due to inadequate response to the radiation and therefore were not included in the overall analysis.

Interdigitation with brachytherapy was done only in 8 out of the 13 patients who received brachytherapy. The main reasons why brachytherapy could not be interdigitated in 3 of our patients were Grade III radiation induced dermatitis and vaginal mucositis, persistent neutropenia and while the other 2 patients did not have adequate response following 40 Gy radiation but brachytherapy was possible after completion of external beam radiotherapy. Therefore another option that could be considered to reduce overall treatment time is to do 2 brachytherapy applications instead of 3 applications with higher dose per fraction. Another advantage of using fewer fractions is patient convenience and improved patient compliance.

Further trials are needed to get an ideal treatment plan so as to get the maximum benefit of chemotherapy as well as that of interdigitated brachytherapy.

Due to inadequate number of patients we need to continue the study to find out the trends of tolerability, as well as documentation of late toxicity. There should be long term follow up for assessing the treatment outcome. Various other regimes of different number of concurrent chemotherapy as well as the number of fractionations and the dose per fraction should be experimented and studied to get an optimum schedule which will allow us to get the maximum benefits of the concurrent chemotherapy as well as that of reaping the full advantage of the possibility of interdigitating HDR brachytherapy along with external radiotherapy so that overall treatment time is less than 8 weeks.

CONCLUSION

&

RECOMMENDATIONS

VII CONCLUSIONS AND RECOMMENDATIONS

In this pilot project done to study the feasibility of interdigitating HDR brachytherapy with Concurrent Chemoirradiation in carcinoma cervix, it was found that there was acute toxicity - hematological toxicity, radiation induced dermatitis and vaginal mucositis which caused significant delay in the completion of the treatment.

The various reasons for not being able to interdigitate brachytherapy with external beam radiotherapy was--

1. Grade 3 and 4 neutropenia
2. Grade 3 radiation induced dermatitis and vaginal mucositis
3. Inadequate response to concurrent chemoirradiation
4. Acute radiation proctitis

With the regime used in our study of 4 cycles of concurrent chemotherapy with cisplatin 40 mg per square meter along with weekly once HDR brachytherapy of 7.2 Gy to point A interdigitating with external radiotherapy only 4 of the 13 patients completed within 8 weeks and none of them completed within the planned 7 weeks. So a reduction in overall treatment time that was aimed for could not be achieved.

Another option that could be tried is to carry out 2 brachytherapy applications with higher dose instead of the 3 fractions as used in this study with a better tolerance and possibility of reducing the overall treatment time. Another advantage of using fewer fractions of brachytherapy would be patient convenience and improved patient compliance.

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APPENDIX

PROFORMA

Patient Characteristics

Name :

Age :

Hospital No : RT NO:

Address :

Contact No :

Occupation :

Presenting Complaints :

1. Bleeding PV Yes (1)/ No (2) Duration
2. Post Coital Bleeding Yes (1)/ No (2) Duration
3. White discharge PV Yes (1)/ No (2) Duration
4. Lower Abdominal pain Yes (1)/ No (2) Duration
5. Low Backache Yes (1)/ No (2) Duration
6. Fever Yes (1)/ No (2) Duration
7. Dyspareunia Yes (1)/ No (2) Duration
8. Fatigue Yes (1)/ No (2) Duration
9. Bladder Symptoms Yes (1)/ No (2) Duration
    a. Dysuria……..
    b. Frequency…….
    c. Burning……
    d. Hematuria……
    e. Incontinence….

10. Bowel Symptoms Yes (1)/ No (2) Duration

a. Bleeding……..

b. Pain…….

c. Frequency.…

Marital Status: 1) Single 2) Married 3) Widow 4) Divorced

Menstrual Status : Premenopausal (1) / Post menopausal (2) Menarche…

Obstetrics G P L A

First Child Birth…

Last Child Birth…

Other Diseases 1 – DM 2 – HT 3 – TB 4 – IHD 5 – Others

Examination

ECOG Ht Wt BSA

CVS Normal (1)/ Abnormal (2)

RS Normal (1)/ Abnormal (2)

CNS Normal (1)/ Abnormal (2)

Abd Normal (1)/ Abnormal (2)

Pelvic Examination:

a) External Genitalia
b) Cervix Anterior lip Posterior lip
c) Fornix Anterior Posterior Right Left
d) Vagina Upper 2/3 Anterior Posterior Right Left
Lower 1/3 Anterior Posterior Right Left
e) Parametrium Right side Not upto pelvic wall/ Upto pelvic wall
Left side Not upto pelvic wall/ Upto pelvic wall
f) Rectal mucosa

Proctoscopy-

Cystoscopy-

Diagnosis Stage

Investigations

1. Pathology
    a. Biopsy 1. Squamous cell carcinoma 2. Adeno carcinoma 3. Others
    b. Differentiation 1. Poor 2. Moderate 3. Well
2. Blood tests Hb TC DC Platelets Creatinine LFT
3. USG Normal (1)/ Abnormal (2)
4. Cxr Normal (1)/ Abnormal (2)

TREATMENT:

CHEMOTHERAPY: Weekly Cisplatin Dose : 4**0 mg/m2 =** ……..mg

Week	RT dose (Gy) completed	Proposed brachytherapy / chemotherapy dates		Actual brachytherapy / chemotherapy dates		Reason for delay
		Dates	Day	Dates	Day	
1						
2						
3						
4						
5						
6						
7						
8						

Delay between the first and second cycle :
Delay between the second and third cycle :
Delay between the third and fourth cycle :
No. of chemotherapy cycles completed :

Delay between the first and second fraction of HDR brachytherapy :
Delay between the second and third fraction of HDR brachytherapy :
No. of brachytherapy applications completed :

Assessment at 40 Gy:

External Beam Radiation Therapy :
Machine: Cobalt / Linac

Energy used: Co -60 , 6MV , 15 MV

Dose / Fractionation :

EBRT - Treatment Time : From
……..…….To…….……

EBRT - Duration of Treatment: ...……weeks …….…....Days

Duration of Breaks during EBRT:

Week 1: …….…….Days
Week 2: …….…….Days
Week 3: …….…….Days
Week 4: …….…….Days
Week 5: …….…….Days
Week 6: …….…….Days
Week 7: …….…….Days
Week 8: …….…….Days

Total days of breaks during EBRT: …….. Days

Reason for the delay:

Brachytherapy : **Dose**

	First fraction	Second fraction	Third fraction
Date of Application			
Point A Dose			
Point B Dose			
Bladder Dose			
R1 dose			
R2 dose			
R3 dose			
Mean Rectal dose			

FOLLOW UP AFTER 6 WEEKS OF COMPLETION OF TREATMENT:

1. Symptoms :
2. Performance status : ECOG ……..
3. Physical Parameters : Height……Weight……BSA..……
4. System Examination :

CVS Normal (1)/ Abnormal (2)

RS Normal (1)/ Abnormal (2)

CNS Normal (1)/ Abnormal (2)

Abd Normal (1)/ Abnormal (2)

Pelvic Examination:

a) External Genitalia
b) Cervix Anterior lip Posterior lip
c) Fornix Anterior Posterior Right Left
d) Vagina Upper 2/3 Anterior Posterior Right Left
Lower 1/3 Anterior Posterior Right Left
e) Parametrium Right side Not upto pelvic wall/ Upto pelvic wall
Left side Not upto pelvic wall/ Upto pelvic wall
f) Rectal mucosa
g) Proctoscopy-

1. Blood tests Hb TC DC Platelets Creatinine LFT
2. USG Normal (1)/ Abnormal (2)
3. Cxr Normal (1)/ Abnormal (2)

APPENDIX II

INFORMED CONSENT FORM

A pilot project to study the feasibility of interdigitating HDR brachytherapy with Concurrent Chemoirradiation in carcinoma cervix I confirm that I have read and understood the information sheet dated ----------for the above study and have had the opportunity to ask questions and to clarify any doubt that I have.

I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving any reason without any medical care or legal rights being affected. I also affirm that no claim for money or any other financial or legal redressal would be made by me as a result of my participation in this study. I understand that the researcher of the clinical trial, the ethics committee and the regulatory authorities will have my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it even if I withdraw from the trial. I agree to this access. However I understand that my identity will not be revealed in any information released to the third parties or published.

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose. I am fully aware of the procedures, its advantages and the possibility of radiation injury that I maybe susceptible. I have been informed about the purpose of the clinical study.

I voluntarily agree to take part in the above study and I understand that I could withdraw from the trial at any time frame.

Signature of Patient / Her Thumb Impression	**Name of Patient**	**Date of Signature**	**Time**
Signature of LAR	**Name of LAR**	**Date of Signature**	**Time**
Signature of Doctor obtaining Consent	**Name of Doctor**	**Date of Signature**	**Time**

Information to the patient

It is for the information that you have been diagnosed to have Cancer of the cervix stage ----- (FIGO). The current recommended therapy is concurrent chemoradiation with weekly administered Cisplatin followed by brachytherapy.

We are inviting you to participate in the study conducted in the Dept. of Radiation Oncology Unit II, Christian Medical College, Vellore in patients with carcinoma of the cervix. It is planned that this study will involve interdigitation of HDR brachytherapy with external radiotherapy along with concurrent chemotherapy with Cisplatin**.**

Many trials have been done in the western world and was found that interdigitating brachytherapy with external radiation leads to reduction in the overall treatment time and later translates into good local control. We try to assess the feasibility of usage of this treatment protocol in routine clinical practice if the side effects are tolerable by the Indian patients and if the response rate achieved is better than the standard practice.

In this study your treatment will be the same as the recommended practice with the only difference of starting brachytherapy before external beam radiation therapy is completed. You are free to withdraw from this study at any point of time. We assure that withdrawal from the study will not affect the rest of your treatment in any way and it will be continued as per the recommended treatment.

Risks associated with Radiation Therapy to the Pelvis

Very Likely

- Low blood counts causing easy bruising
- Shortening and narrowing of the vagina
- Pain with sexual intercourse
- Tiredness near the end of treatment
- Diarrhea , Nausea and/or vomiting
- Stomach pain that feels like bad heartburn or an ulcer and that may make eating or drinking difficult; if you become dehydrated, you may need toreceive fluids through your vein
- Poor digestion of food
- Weight loss; if this is severe, you may need a tube placed into your stomach to provide nutrition
- Rectal irritation
- Urinary frequency and difficulty
- Loss of pubic hair
- Reddening and irritation of the skin in the treatment area

Less Likely But Serious

- Rectal ulcer
- Bleeding or narrowing of the rectum
- Bloody urine
- Pain, bleeding, and/or blockage of the stomach or other parts of the digestive system
- Ureteral (tube connecting kidneys to the bladder) obstruction
- Fistula (opening) forming between pelvic tissues

Reproductive risks

This study may be harmful to an unborn child. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy

test prior to participating in this study. The results will be made available to you

prior to the initiation of this study. Ask about counseling and more information

about preventing pregnancy. You should not nurse your baby while on this study.

Radiation to the pelvis will cause sterility, and you will not be able to become

pregnant after treatment. Young women will go through menopause, and

medication will be given to help with the symptoms of menopause.

Risks Associated with Cisplatin

Very Likely

Decrease in blood counts which can lead to a risk of infection and bleeding.

Loss of appetite and/or taste; metallic taste in your mouth

Nausea and/or vomiting

Fatigue

Hearing loss or ringing in the ears

Numbness or tingling in the hands or feet

Less Likely

Muscle cramps or spasm

Loss of coordination

Involuntary movements or shaking

Loss of muscle or nerve function which may cause weakness or numbness in your hands and feet

Facial swelling

Less Likely, But Serious

A decrease in the kidneys' ability to handle the body's waste, which may be permanent.

Allergic reactions which can cause difficulty breathing, fast heartbeat, and sweating

Decrease in liver function

Another cancer called Acute Leukemia

PERSONS TO CONTACT FOR FURTHER INFORMATION AND IN IMMEDIATE NEED:

Dr Subhashini John, Department of Radiation Oncology, Christian Medical College, Vellore

Dr Rajesh I, Department of Radiation Oncology, Christian Medical College, Vellore

Dr Rajesh B, Department of Radiation Oncology, Christian Medical College, Vellore

Dr Patricia S, Department of Radiation Oncology, Christian Medical College, Vellore

Taking part in this study is completely your choice. If you decide to participate, you will be asked to sign the consent form. Kindly sign the consent form only when you understand the information given in the form and have had your questions answered to your complete satisfaction and understanding. You will be given a copy of the signed form which you should keep for your personal records.

Any questions about the study or clarification can be cleared with Dr. David Mathew or with the co-investigators of this trial.

COSTS: There is no extra cost to be paid for this study. Patients have to pay for the radiation therapy, Brachytherapy and concurrent chemotherapy as per the current practice.

PAYMENT: You will not be paid for participating in this trial.

PARTICIPANT'S STATEMENT:

I have read the consent form and the information sheet and have discussed with Dr_____ about the study method and procedures. I have been given the opportunity to ask questions which have been answered to my satisfaction. I understand that my participation in this study is voluntary and that I may refuse to participate. I also understand that if, for any reason, I wish to withdraw my participation, I will be free to do so and that this will have no effect on my further treatment.

I hereby declare that I have been fully informed about the study with its risks and benefits and consent to participate in this trial with my full consciousness.

Signature of Patient / Her Thumb Impression	**Name of Patient**	**Date of Signature**	**Time**
Signature of LAR	**Name of LAR**	**Date of Signature**	**Time**
Signature of Doctor obtaining Consent	**Name of Doctor**	**Date of Signature**	**Time**